37 CFR 1.663

H1

41. (Amended) The replication defective recombinant adenovirus of claim 40, wherein the promoter is selected from the group consisting of an adenovirus E1A promoter, [a] an adenovirus MLP promoter, a CMV promoter, and an RSV LTR promoter.

REMARKS

Claims 31 and 32 have been canceled without prejudice, solely to expedite prosecution of the application. Claims 1-3, 6, 9-30, and 33-41 are currently pending in this application. Claim 41 has been amended to more particularly point out and distinctly claim that which Applicants regard as their invention and with the expectation that, following the Examiner's suggestions, the amendment places the claim in condition for allowance. Support for amended claim 41 is found on page 2, lines 1-5, page 8, lines 16-36, and page 17, line 14 of the Specification. No new matter has been added. All of the claims under consideration, as amended, are presented as an Appendix attached hereto.

Summary of the Examiner's Final Office Action

The Final Office Action dated November 20, 1998 contains the following rejections:

(1) Claim 41 Under Section 112, Second Paragraph; and
(2) Claims 31 and 32 Under Section 102(e) as being allegedly anticipated by Gregory *et al.*

Applicants note that the Examiner has stated that claims 1-3, 6, 9-30, and 33-40 are allowed (Office Action Summary and page 3, Final Office Action). In addition, he has indicated that claim 41 would be allowable if rewritten to overcome the rejection under 35 U.S.C. 112, second paragraph (page 3, Final Office Action). Each of the issues raised by the Examiner are discussed below. Applicants believe that the foregoing amendment and the following remarks respond completely to the objections and rejections. Applicants further believe the claims are in condition for allowance.

(1) Rejection of Claim 41 Under Section 112, Second Paragraph

Applicants have amended claim 41 to obviate the Examiner's objection. Applicants respectfully traverse this rejection to the extent that Applicants submit that the claimed invention as recited in amended claim 41 is definite under Section 112, second paragraph. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

In response to the Examiner's suggestions, Applicants have amended claim 41 to recite that the E1A and MLP promoters are from an adenovirus. In addition, claim 41 has been amended to recite an RSV LTR promoter. With regard to the Examiner's statement that a "CMV promoter" may be interpreted as either a "cytomegalovirus promoter" or a "cucumber mosaic virus promoter" (page 2, Final Office Action), Applicants submit respectfully that the term "CMV promoter", taken in the context of Applicants' Specification, would be understood by one skilled in the relevant art to represent a promoter derived from cytomegalovirus. Applicants submit that "CMV" is a term which is commonly used in the art to represent cytomegalovirus. Applicants' invention is directed to adenoviruses which infect animal cells. Applicants submit that cucumber mosaic viruses do not infect animal cells. Due to the inability of cucumber mosaic viruses to infect animal cells, the skilled artisan would not expect that a cucumber mosaic virus promoter would work in an animal cell. Therefore, the CMV promoter described in Applicants' Specification (see page 8, lines 16-36) and recited in claim 41 would be understood by the skilled artisan to represent a promoter derived from cytomegalovirus.

In view of the foregoing amendment and remarks, the Examiner's rejection is obviated in part and overcome in part. Applicants submit that claim 41 is definite under 35 USC § 112, second paragraph. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(2) Rejection of Claims 31 and 32 Under Section 102(e)

The Examiner has rejected claims 31 and 32 under 35 U.S.C. § 102(e), as being anticipated by Gregory *et al.* Applicants have canceled claims 31 and 32 without prejudice in the instant application. Therefore, this rejection is moot. Applicants request respectfully that the rejection be reconsidered and withdrawn.

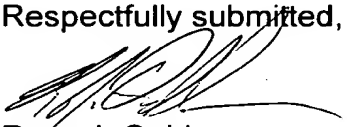
Conclusion

In view of the foregoing amendments and remarks, Applicants submit that claims 1-3, 6, 9-30, and 33-41 satisfy the requirements of 35 U.S.C. § 112 and are in condition for allowance. Favorable reconsideration and an action passing this case to issue are therefore requested respectfully. If a telephone interview would be of assistance in advancing prosecution of this application, Applicant's attorney invites the Examiner to contact him at the number provided below.

Rhône-Poulenc Rorer Inc.
Legal-Patents #3C43
P.O. Box 5093
Collegeville, PA 19426-0997
Telephone: (610) 454-3883
Facsimile: (610) 454-3808

Dated: 5-17-99

Respectfully submitted,



Ross J. Oehler
Attorney for Applicants
Registration No. 33,270

APPENDIX
U.S. Patent Application Serial No. 08/397,225
" DEFECTIVE ADENOVIRUS VECTORS AND USE THEREOF IN GENE THERAPY"
RPR File No. EX93015G1-US
Pending Claims

1. (Five Times Amended) A replication defective recombinant adenovirus comprising

ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,

wherein E1 genes have been rendered non-functional by deletion, and wherein either E2 or E4 genes, but not both, have been rendered non-functional by deletion.

2. (Three Times Amended) A replication defective recombinant adenovirus comprising

ITR sequences,
an encapsulation sequence,
and a heterologous DNA sequence,

wherein E1 genes have been rendered non-functional by deletion, wherein E2 or E4 genes have been rendered non-functional by deletion, and wherein adenovirus sequences are from a canine adenovirus.

3. (Four Times Amended) The replication defective recombinant adenovirus according to claim 1, wherein adenovirus sequences are from a human group C adenovirus.

6. (Four Times Amended) The replication defective recombinant adenovirus according to claim 1, wherein late genes L1-L5 have been rendered non-functional by deletion.

9. (Four Times Amended) The replication defective recombinant adenovirus according to claim 1, wherein E3 genes have been rendered non-functional by deletion.

10. (Four Times Amended) The replication defective recombinant adenovirus according to claim 9, wherein L5 has been rendered non-functional by deletion.

11. (Three Times Amended) A replication defective recombinant adenovirus comprising

ITR sequences,
an encapsulation sequence,
and a heterologous DNA sequence,

and a functional E3 gene under the control of a heterologous promoter, wherein E1 genes have been rendered non-functional by deletion, and wherein E2 or E4 genes have been rendered non-functional by deletion.

12. (Four Times Amended) The replication defective recombinant adenovirus according to claim 1, wherein the heterologous DNA sequence is selected from the group consisting of a therapeutic gene and a gene encoding an antigenic peptide.

13. (Five Times Amended) The replication defective recombinant adenovirus according to claim 12, wherein the heterologous DNA is a therapeutic gene which encodes a product selected from the group consisting of an enzyme, a blood protein, a hormone, a lymphokine, a growth factor, a neurotrophic factor, an apolipoprotein, a dystrophin, a minidystrophin, a tumor suppressor, and a coagulation factor.

14. (Three Times Amended) The replication defective recombinant adenovirus according to claim 1, wherein the heterologous DNA is transcribed into an antisense RNA, which is complementary to a cellular mRNA and blocks translation of the cellular mRNA into protein in an infected cell.

15. (Three Times Amended) The replication defective recombinant adenovirus according to claim 12, wherein the heterologous DNA encodes an antigenic peptide which generates an immune response against a microorganism, a tumor, or a virus when introduced into a human.

16. (Three Times Amended) The replication defective recombinant adenovirus according to claim 15, wherein the heterologous DNA encodes an antigenic peptide which generates an immune response against a virus selected from the group consisting of an Epstein Barr virus, an HIV virus, a hepatitis B virus, and a pseudo-rabies virus when introduced into a human.

17. (Three Times Amended) The replication defective recombinant adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a sequence which permits expression of the heterologous DNA sequence in an infected cell.

18. (Three Times Amended) The replication defective recombinant adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a signal sequence, which directs a product encoded by the heterologous DNA sequence into a secretory pathway of a target cell.

19. (Three Times Amended) A cell line comprising, integrated into its genome, adenovirus genes necessary to complement the replication defective

recombinant adenovirus according to claim 1, wherein one of the complementing genes is under the control of an inducible promoter.

20. (Four Times Amended) The cell line according to claim 19, wherein it comprises, in its genome, an E1 gene and an E2 gene wherein the E2 gene is under the control of an inducible promoter.

21. (Four Times Amended) The cell line according to claim 20, wherein it additionally comprises an E4 gene from an adenovirus, wherein the E4 gene is placed under the control of an inducible promoter.

22. (Four Times Amended) The cell line according to claim 19, wherein it comprises, in its genome, an E1 gene and an E4 gene wherein the E4 gene is under the control of an inducible promoter.

23. (Three Times Amended) The cell line according to claim 19, further comprising a glucocorticoid receptor gene.

24. (Four Times Amended) The cell line according to claim 19, wherein it comprises E2 and E4 genes and the E2 and E4 genes are under the control of an inducible promoter.

25. (Three Times Amended) The cell line according to claim 19, wherein the inducible promoter is an LTR promoter of MMTV.

26. (Four Times Amended) The cell line according to claim 19, comprising a gene encoding the 72 K protein of E2, wherein the 72 K protein encoding gene is placed under the control of an inducible promoter.

27. (Three Times Amended) The cell line according to claim 19, wherein it is constructed from human embryonic kidney cell line 293.

28. (Three Times Amended) A composition comprising the replication defective recombinant adenovirus according to claim 1 and a pharmaceutically acceptable vehicle.

29. (Three Times Amended) A composition comprising the replication recombinant adenovirus according to claim 10 and a pharmaceutically acceptable vehicle.

30. (Three Times Amended) The composition according to claim 28, wherein the vehicle is pharmaceutically acceptable for an injectable formulation.

33. (Twice Amended) The cell line according to claim 19, comprising open reading frames ORF6 and ORF6/7 of E4, wherein the open reading frames are under the control of an inducible promoter.

34. (Four Times Amended) A replication defective recombinant adenovirus comprising

ITR sequences,

an encapsulation sequence,
a heterologous DNA sequence, and
an E2 region,
wherein the E2 region is the sole adenoviral early region.

35. (Four Times Amended) A replication defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
an E4 region,
wherein the E4 region is the sole adenoviral region.

36. (Amended) A replication defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
an E4 coding region,
wherein E4 genes have been rendered non-functional by one or more modifications outside of the E4 coding region.

37. (Amended) The replication defective recombinant adenovirus according to claim 36, wherein the E4 genes have been rendered non-functional by deletion of all or part of the promoter region for E4 transcription.

38. (Amended) The replication defective recombinant adenovirus according to claim 36 wherein the E4 genes have been rendered non-functional by substitution of one or more bases in the E4 genes.

39. (Amended) The replication defective recombinant adenovirus according to claim 38 wherein the E4 genes have been rendered non-functional by one or more genetic modifications within regions responsible for E4 gene expression or transcriptional regulation, or both.

40. The replication defective recombinant adenovirus according to claim 17, wherein the sequence permitting expression of the heterologous DNA sequence is a promoter.

41. (Amended) The replication defective recombinant adenovirus of claim 40, wherein the promoter is selected from the group consisting of an adenovirus E1A promoter, an adenovirus MLP promoter, a CMV promoter, and an RSV LTR promoter.